(e) *Test notes.* The following notes appy to the data requirements table in paragraph (d) of this section.

1. The Agency has waived the requirement to submit product performance data unless the pesticide product bears a claim to control pest microorganisms that pose a threat to human health and whose presence cannot readily be observed by the user including, but not limited to, microorganisms infectious to man in any area of the inanimate environment, or a claim to control vertebrates (such as rodents, birds, bats, canids, and skunks) that may directly or indirectly transmit diseases to humans. However each registrant must ensure through testing that his product is efficacious when used in accordance with label directions and commonly accepted pest control practices. The Agency reserves the right to require, on a case-by-case basis, submission of product performance data for any pesticide product registered or proposed for registration.

2. [Reserved]

Subpart F—Toxicology

§ 158.500 Toxicology data requirements table.

(a) *General.* Sections 158.100 through 158.130 describe how to use the data table in paragraph (d) of this section to determine the toxicology data requirements for a particular pesticide product. Notes that apply to an individual test and include specific conditions, qualifications, or exceptions to the designated test in the table are listed in paragraph (e) of this section.

(b) *Use patterns.* (1) Food use patterns include products classified under the general use patterns of terrestrial food crop use, terrestrial feed crop use, aquatic food crop use, greenhouse food crop use, and indoor food use.

(2) Nonfood use patterns include products classified under the general use patterns of terrestrial nonfood crop use, aquatic nonfood use, greenhouse nonfood crop use, forestry use, residential outdoor use, and indoor nonfood use.

(c) *Key.* R=Required; CR=Conditionally required; NR=Not required; MP=Manufacturing-use product; EP=End-use product; TGAI=Technical grade of the active ingredient; PAI=Pure active ingredient; PAIRA=Pure active ingredient radiolabeled; Choice=Choice of several test substances depending on study required.

(d) *Table.* The following table lists the toxicology data requirements. The table notes are shown in paragraph (e) of this section.

TABLE—TOXICOLOGY DATA REQUIREMENTS

Guideline Number	Data Requirements	Use Pattern		Test substance to support		Test Note No.
		Food	Nonfood	MP	EP	
Acute Testing						
870.1100	Acute oral toxicity - rat	R	R	TGAI and MP	TGAI, EP, and possibly diluted EP	1, 2
870.1200	Acute dermal toxicity	R	R	TGAI and MP	TGAI, EP	1, 2, 3
870.1300	Acute inhalation toxicity - rat	R	R	TGAI and MP	TGAI and EP	4
870.2400	Primary eye irritation - rabbit	R	R	TGAI and MP	TGAI and EP	3
870.2500	Primary dermal irritation	R	R	TGAI and MP	TGAI and EP	1, 3
870.2600	Dermal sensitization	R	R	TGAI and MP	TGAI and EP	3, 5
870.6100	Delayed neurotoxicity (acute) - hen	CR	CR	TGAI	TGAI	6
870.6200	Acute neurotoxicity - rat	R	R	TGAI	TGAI	7

TABLE—TOXICOLOGY DATA REQUIREMENTS—Continued

Guideline Number	Data Requirements	Use Pattern		Test substance to support		Test Note No.
		Food	Nonfood	MP	EP	
Subchronic Testing						
870.3100	90–day Oral - rodent	R	CR	TGAI	TGAI	8, 9
870.3150	90–day Oral - non-rodent	R	CR	TGAI	TGAI	36
870.3200	21/28–day Dermal	R	NR	TGAI	TGAI and EP	10, 11
870.3250	90–day Dermal	CR	R	TGAI	TGAI and EP	11, 12
870.3465	90–day Inhalation - rat	CR	CR	TGAI	TGAI	13, 14
870.6100	28–day Delayed neurotoxicity-hen	CR	CR	TGAI	TGAI	6, 15
870.6200	90–day Neurotoxicity - rat	R	R	TGAI	TGAI	7, 16
Chronic Testing						
870.4100	Chronic oral - rodent	R	CR	TGAI	TGAI	17, 18, 19
870.4200	Carcinogenicity - two rodent species - rat and mouse preferred	R	CR	TGAI	TGAI	9, 17, 18, 19, 20, 21
Developmental Toxicity and Reproduction						
870.3700	Prenatal Developmental toxicity - rat and rabbit, preferred	R	R	TGAI	TGAI	22, 23, 24, 25, 26
870.3800	Reproduction and fertility effects	R	R	TGAI	TGAI	26, 27, 29
870.6300	Developmental neurotoxicity	CR	CR	TGAI	TGAI	27, 28, 29
Mutagenicity Testing						
870.5100	Bacterial reverse mutation assay	R	R	TGAI	TGAI	30
870.5300 870.5375	*In vitro* mammalian cell assay	R	R	TGAI	TGAI	30, 31
870.5385 870.5395	*In vivo* cytogenetics	R	R	TGAI	TGAI	30, 32
Special Testing						
870.7485	Metabolism and pharmacokinetics	R	CR	PAI or PAIRA	PAI or PAIRA	33
870.7200	Companion animal safety	CR	CR	NR	TGAI or EP	34
870.7600	Dermal penetration	CR	CR	Choice	Choice	35
870.7800	Immunotoxicity	R	R	TGAI	TGAI	

(e) *Test notes.* The following test notes apply to the requirements in the table to paragraph (d) of this section:

1. Not required if test material is a gas or a highly volatile liquid.

2. Diluted EP testing is required to support the end product registration if results using the EP meet the criteria for restricted use classification under §152.170(b) or special review consideration under §154.7(a)(1).

3. Not required if the test material is corrosive to skin or has a pH of less than 2 or greater than 11.5.

4. Required if the product consists of, or under conditions of use will result in, a respirable material (e.g., gas, vapor, aerosol, or particulate).

5. Required if repeated dermal exposure is likely to occur under conditions of use.

6. Required if the test material is an organophosphorus substance, which includes uncharged organophosphorus esters; thioesters or anhydrides of organophosphoric, organophosphonic, or organophosphoramidic acids; or of related phosphorothioic, phosponothioic, or phosphorothioamidic acids; or is structurally related to other substances that may cause the delayed neurotoxicity sometimes seen in this class of chemicals.

7. As determined by the Agency, additional measurements may also be required, such as cholinesterase activity for certain pesticides, e.g., organophosphates and some carbamates. The route of exposure must correspond with the primary route of exposure.

8. Required for nonfood use pesticides if oral exposure could occur.

9. The 90–day study is required in the rat for hazard characterization (possibly endpoint selection) and dose-setting for the chronic/carcinogenicity study. It is not required in the mouse, but the Agency would strongly encourage the registrant to conduct a 90–day range finding for the purposes of dose selection for the mouse carcinogenicity study to achieve adequate dosing and an acceptable study. The registrant is also encouraged to consult with the Agency on the results of the 90–day mouse study prior to conducting the carcinogenicity study.

10. Required for agricultural uses or if repeated human dermal exposure may occur. Not required if an acceptable 90–day dermal toxicity study is performed and submitted.

11. EP testing is required if the product, or any component of it, may increase dermal absorption of the active ingredient(s) as determined by testing using the TGAI, or increase toxic or pharmacologic effects.

12. Required for food uses if either of the following criteria is met:

(i) The use pattern is such that the dermal route would be the primary route of exposure; or

(ii) The active ingredient is known or expected to be metabolized differently by the dermal route of exposure than by the oral route, and a metabolite is the toxic moiety.

13. Required if there is the likelihood of significant repeated inhalation exposure to the pesticide as a gas, vapor, or aerosol.

14. Based on estimates of the magnitude and duration of human exposure, studies of shorter duration, e.g., 21– or 28–days, may be sufficient to satisfy this requirement. Registrants should consult with the Agency to determine whether studies of shorter duration would meet this requirement.

15. Required if results of acute neurotoxicity study indicate significant statistical or biological effects, or if other available data indicate the potential for this type of delayed neurotoxicity, as determined by the Agency.

16. All 90–day subchronic studies in rats can be designed to simultaneously fulfill the requirements of the 90–day neurotoxicity study using separate groups of animals for testing. Although the subchronic guidelines include the measurement of neurological endpoints, they do not meet the requirement of the 90–day neurotoxicity study.

17. Required if either of the following are met:

(i) The use of the pesticide is likely to result in repeated human exposure over a considerable portion of the human lifespan, as determined by the Agency;

(ii) The use requires a tolerance or an exemption from the requirement of a tolerance.

18. Based on the results of the acute and subchronic neurotoxicity studies, or other available data, a combined chronic toxicity and neurotoxicity study may be required.

19. Studies which are designed to simultaneously fulfill the requirements of both the chronic oral and carcinogenicity studies (*i.e.*, a combined study) may be conducted. Minimum acceptable study durations are:

(i) Chronic rodent feeding study (food use) - 24 months.

(ii) Chronic rodent feeding study (nonfood use) - 12 months.

(iii) Mouse carcinogenicity study - 18 months.

(iv) Rat carcinogenicity study - 24 months.

20. Required if any of the following, as determined by the Agency, are met:

(i) The use of the pesticide is likely to result in significant human exposure over a considerable portion of the human life span which is significant in terms of either frequency, duration, or magnitude of exposure;

(ii) The use requires a tolerance or an exemption from the requirement of a tolerance; or

(iii) The active ingredient, metabolite, degradate, or impurity (a) is structurally related to a recognized carcinogen, (b) causes mutagenic effects as demonstrated by *in vitro* or *in vivo* testing, or (c) produces a morphologic effect in any organ (e.g., hyperplasia, metaplasia) in subchronic studies that may lead to a neoplastic change.

21. If this study is modified or waived, a subchronic 90–day oral study conducted in the same species may be required.

22. Testing in two species is required for all uses.

23. The oral route, by oral intubation, is preferred unless the chemical or physical properties of the test substance or the pattern of exposure suggests a more appropriate route of exposure.

24. Additional testing by other routes may be required if the pesticide is determined to be a prenatal developmental toxicant after oral dosing.

25. May be combined with the 2–generation reproduction study in rodents by utilizing a second mating of the parental animals in either generation.

26. Required to support products intended for food uses and to support products intended for nonfood uses if use of the product is likely to result in significant human exposure over a portion of the human life span in terms of frequency, magnitude or duration of exposure.

27. An information-based approach to testing is preferred, which utilizes the best available knowledge on the chemical (hazard, pharmacokinetic, or mechanistic data) to determine whether a standard guideline study, an enhanced guideline study, or an alternative study should be conducted to assess potential hazard to the developing animal, or in some cases to support a waiver for such testing. Registrants should submit any alternative proposed testing protocols and supporting scientific rationale to the Agency prior to study initiation.

28. Study required using a weight-of-evidence approach considering:

(i) The pesticide causes treatment-related neurological effects in adult animal studies (*i.e.*, clinical signs of neurotoxicity, neuropathology, functional or behavioral effects).

(ii) The pesticide causes treatment-related neurological effects in developing animals, following pre- and postnatal exposure (*i.e.*, nervous system malformations or neuropathy, brain weight changes in offspring, functional or behavioral changes in the offspring).

(iii) The pesticide elicits a causative association between exposures and adverse neurological effects in human epidemiological studies.

(iv) The pesticide evokes a mechanism that is associated with adverse effects on the development of the nervous system (e.g., SAR relationship to known neurotoxicants, altered neuroreceptor or neurotransmitter responses).

29. The use of a combined study that utilizes the 2–generation reproduction study in rodents as a basic protocol for the addition of other endpoints or functional assessments in the immature animal is encouraged.

30. At a minimum, an initial battery of mutagenicity tests with possible confirmatory testing is required. Other relevant mutagenicity tests that may have been performed, plus a complete reference list must also be submitted.

31. Choice of assay using either:

(i) Mouse lymphoma L5178Y cells, thymidine kinase (tk) gene locus, maximizing assay conditions for small colony expression or detection;

(ii) Chinese hamster ovary (CHO) or Chinese hamster lung fibroblast (V79) cells, hypoxanthine-guanine phosphoribosyl transferase (hgprt) gene locus, accompanied by an appropriate *in vitro* test for clastogenicity; or

(iii) CHO cells strains AS52, xanthine-guanine phosphoribosyl transferase (xprt) gene locus.

32. The micronucleus rodent bone marrow assay is preferred; however, rodent bone marrow assays using metaphase analysis (aberrations) are acceptable.

33. Required when chronic or carcinogenicity studies are required. May be required if significant adverse effects are seen in available toxicology studies and these effects can be further elucidated by metabolism studies.

34. May be required if the product's use will result in exposure to domestic animals through, but not limited to, direct application.

35. A risk assessment assuming that dermal absorption is equal to oral absorption must be performed to determine if the study is required, and to identify the doses and duration of exposure for which dermal absorption is to be quantified.

36. A 1–year non-rodent study (*i.e.*, 1–year dog study) would be required if the Agency finds that a pesticide chemical is highly bioaccumulating and is eliminated so slowly that it does not achieve steady state or sufficient tissue concentrations to elicit an effect during a 90–day study. EPA would require the appropriate tier II metabolism and pharmacokinetic studies to evaluate more precisely bioavailability, half-life, and steady state to determine if a longer duration dog toxicity study is needed.

§ 158.510 Tiered testing options for nonfood pesticides.

For nonfood use pesticides only, applicants have two options for generating and submitting required toxicology (§ 158.500) and human exposure (§ 158.1020, § 158.1070, and § 158.1410) studies. Applicants are to select one of the following:

(a) Acute, subchronic, chronic, and other toxicological studies on the active ingredient must be submitted together. The specific makeup of the set of toxicology study requirements is based on the anticipated exposure to the pesticide as determined by the Agency. If hazards are identified based upon review of these studies, specific exposure data will be required to evaluate risk.

(b) Certain toxicological and exposure studies must be submitted simultaneously with the toxicology data submitted in a tiered system. Exposure data must be submitted along with